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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/603,800

06/26/2003

Junji Hamuro

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10/18/2006

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EXAMINER

NGUYEN, QUANG

ART UNIT

PAPER NUMBER

1633

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/603,800

Applicant(s)

HAMURO ET AL.

Examiner

Quang Nguyen, Ph.D.

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 22 September 2006.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 21-29 and 33-43 is/are pending in the application.
- 4a) Of the above claim(s) 24-26 and 40-42 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 21-23, 27-29, 33-39 and 43 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

Applicant's amendment filed on 9/22/06 was entered.

Claims 21-29, 33-43 are pending in the present application.

Applicants elected previously with traverse the following species: (a) macrophages as a cell species; (b) N,N'-diacylcystine as a species of a substance; and (c) corneal epithelium as a species of an organ, in the reply filed on 12/23/04.

Claims 24-26 and 40-42 were withdrawn previously from further consideration because they are directed to non-elected species. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

***Accordingly, amended claims 21-23, 27-29, 33-39 and new claim 43 are examined on the merits herein with the above elected species.***

### ***Claim Objections***

Amended claim 21 is objected to because of the lack of an article in front of the term "corneal epithelium allograft" on line 2 of the claim. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Art Unit: 1633

Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

Amended claim 28 recites the limitation "the whole corneal epithelium" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim. This is because prior to this limitation, there is no recitation of any whole corneal epithelium in either claim 28 or in independent claim 21. Which particular whole corneal epithelium do Applicants refer to? Clarification is requested because the metes and bounds of the claim are not clearly determined. For the purpose of a compact prosecution, the examiner interprets the amended claim to refer to an allograft of any whole corneal epithelium, and as such the following prior art is still applied.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 21-23, 27-29 and 33-39 are still rejected under 35 U.S.C. 103(a) as being unpatentable over Hamuro et al. (EP 1 004 302 A2, IDS) in view of Hegde et al. (Invest. Ophthalmol. Vis. Sci. 41:3341-3347, 2000) and Isseroff et al. (US 2002/0039788 A1) for the same reasons already set forth in the Office Action mailed on 3/23/06 (pages 3-7). ***For Applicant's convenience, the same rejection is restated below.***

Hamuro et al already disclose N, N'-diacetylcystine [(NAC)<sub>2</sub>] to be a substance having the activity of reducing the content of reductive glutathione in the macrophages (page 9, paragraphs 49-51; page 5, paragraph 21), and that this immunomodulator can be included in a drug, a food (e.g., food for medical care, a health food or a special sanitary food, a toothpaste, a chewing gum and the like), a nutrient (e.g., vitamin and calcium preparations) and an infusion such as a high calory infusion, a physiological saline solution and blood preparations (see abstract; page 2, paragraphs 1-2; page 3, paragraph 10; page 6, paragraph 22). Please note that a physiological saline solution, a high calory infusion, a chewing gum is considered to be a pharmaceutically acceptable carrier. Hamuro et al. further teach the immunomodulator is useful as an immunosuppressant against human immunological diseases such as hepatic cirrhosis, hepatitis, diabetes, gastrointestinal inflammatory diseases such as inflammatory bowel

diseases (e.g., ulcerative colitis and Crohn disease), autoimmune diseases and allergic diseases such as hypersensitive interstitial pneumonia, pulmonary fibrosis, chronic rheumatoid arthritis, asthma and cutaneous atopy (see abstract). Hamuro et al also disclose that the immunomodulator can be applied not only to patients suffering from attacked or chronic diseases but also to high-risk persons suffering from adult diseases (page 10, last sentence of paragraph 57). The dose of the substance having an activity of changing the content of reductive glutathione as an active ingredient,  $(\text{NAC})_2$  for this instance, is selected depending on the conditions of the patients or the like to which the substance is administered or the use purpose, including the dosage between 1 and 5,000 mg (oral drug), preferably between 10 and 500 mg/day, which is within the recited dose ranging from 1 mg to 10 g (page 10, top of paragraph 54). Non-limited examples showed that  $(\text{NAC})_2$  was administered intraperitoneally at 20  $\mu\text{g}/0.5\text{ml/h}$  each for 20 h in mice on day 1 and day 2 to induce oxidative macrophages (example 9), and that the administration of  $(\text{NAC})_2$  inhibits delayed type hypersensitivity reaction to ovalbumin (example 10) as well as inhibition of spontaneous inflammatory bowel diseases in  $\gamma\text{c}$  knockout mice having intestinal inflammation similar to that of humans (example 13) and suppression of joint swelling in a rat adjuvant-induced arthritis (example 19).

Hamuro et al do not teach specifically the use of N, N'-diacetylcystine  $[(\text{NAC})_2]$  to suppress a rejection to a minor antigen in any allograft, particularly a corneal epithelium allograft in a recipient in need thereof, even though they teach that  $(\text{NAC})_2$  is useful as **an immunosuppressant** against various human immunological diseases such as

Art Unit: 1633

hepatic cirrhosis, hepatitis, diabetes, gastrointestinal inflammatory diseases such as inflammatory bowel diseases (e.g., ulcerative colitis and Crohn disease), autoimmune diseases and allergic diseases such as hypersensitive interstitial pneumonia, pulmonary fibrosis, chronic rheumatoid arthritis, asthma and cutaneous atopy, and particularly (NAC)<sub>2</sub> has been shown to inhibit a delayed type hypersensitivity reaction to ovalbumin (example 10) in a mouse model.

At the effective filing date of the present application (12/26/00) Hegde et al already taught that the relevant immune response during corneal allograft rejection is a donor-specific delayed type hypersensitivity (DTH) reaction (see at least the abstract). Hegde et al further teach that except in high risk cases, neither HLA typing nor systemic immunosuppression is performed routinely and although typical 2-year survival rates for initial grafts onto avascular graft beds are in excess 90%, approximately 4000 corneal grafts fail each year in the United States because of immunological rejection (page 3341, col. 1, first paragraph).

Isseroff et al also taught methods of treating a damaged or diseased ocular surface by applying a corneal epithelial composite graft to the damaged or diseased ocular surface, wherein the graft comprises a plurality of corneal epithelial cells, including autologous or allogeneic cells (see at least paragraphs 18-20, 35 and 47-48). Isseroff et al further disclose that although patients 13 and 14 had successful allografts complications associated with Cyclosporin A resulted in either the decrease or temporarily discontinuation of the immunosuppressant drug (bottom of paragraph 47).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Hamuro et al by using N, N'-diacetylcystine [(NAC)<sub>2</sub>] as an immunosuppressant to suppress a rejection to a minor antigen in an allograft, including a corneal epithelium allograft in a recipient in need thereof in light of the teachings of Hegde et al. and Isseroff et al.

An ordinary skilled artisan would have been motivated to carry out the above modification for the following reasons. Firstly, (NAC)<sub>2</sub> is taught to be useful as an immunosuppressant against various human inflammatory immunological diseases by Hamuro et al., and an allograft rejection is considered to be an inflammatory immunological disease. Secondly, it has been shown to inhibit successfully a delayed type hypersensitivity reaction *in vivo* and the DTH reaction has been demonstrated by Hegde et al to be the relevant immune response responsible for corneal allograft rejection. Thirdly, due to the apparent non-toxicity of (NAC)<sub>2</sub> because of its inclusion in food (e.g., food for medical care, a health food or a special sanitary food, a toothpaste, a chewing gum and the like), a nutrient (e.g., vitamin and calcium preparations) and an infusion such as a high calory infusion, the use of (NAC)<sub>2</sub> would be free of complications associated with conventional immunosuppressant drugs such as Cyclosporin A as already noted by both Hegde et al. and Isseroff et al. Fourthly, the use of (NAC)<sub>2</sub> as a complication-free immunosuppressant would reduce the rejection of corneal epithelial allografts in a patient in need thereof.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Hamuro et al., Hegde et al. and Isseroff et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

### ***Response to Argument***

Applicants' arguments related to the above rejection in the Amendment filed on 9/22/06 (pages 7-9) have been fully considered, but they are not found to be persuasive.

With respect to the Hamuro et al reference, Applicants argue that the reference fails to disclose or suggest treating corneal epithelial allograft rejection. With respect to the Hegde et al reference, Applicants argue that this reference also fails to disclose or suggest cornea epithelial allograft because it specifically relates to cornea rejection which is not the same as cornea epithelial allograft rejection. With respect to Isseroff et al, Applicants argue that this reference merely discloses corneal epithelial allografts and some problems associated therewith, but does nothing to compensate for the deficiencies in Hamuro et al or Hegde et al reference. Applicants further argue that the disclosures of Hamuro et al, Hegde et al, and Isseroff et al provide a motivation to experiment or could be viewed as making it "obvious to try" to arrive at the present invention, and "obvious to try" has long been held not to constitute obviousness, and a general incentive does not make obvious of a particular result nor does the existence of

techniques by which those efforts can be carried out. Finally, Applicants argue that the disclosures of Hamuro et al, Hegde et al, and even if combined with Isseroff et al fail to provide motivation to suppress a rejection to a minor corneal epithelium allograft in a subject in need thereof, fail to disclose all the limitations of the presently claimed invention and that there is no reasonable expectation of success.

1. Please note that the above rejection is a 103 rejection. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

2. Hamuro et al clearly taught that N, N'-diacetylcystine [(NAC)<sub>2</sub>] is a substance having the activity of reducing the content of reductive glutathione in the macrophages (page 9, paragraphs 49-51; page 5, paragraph 21), and that this immunomodulator can be included in a drug, a food (e.g., food for medical care, a health food or a special sanitary food, a toothpaste, a chewing gum and the like), a nutrient (e.g., vitamin and calcium preparations) and an infusion such as a high calory infusion, a physiological saline solution and blood preparations (see abstract; page 2, paragraphs 1-2; page 3, paragraph 10; page 6, paragraph 22). Hamuro et al further taught the immunomodulator is useful as an immunosuppressant against human immunological diseases such as hepatic cirrhosis, hepatitis, diabetes, gastrointestinal inflammatory diseases such as inflammatory bowel diseases (e.g., ulcerative colitis and Crohn disease), autoimmunological diseases and allergic diseases such as

Art Unit: 1633

hypersensitive interstitial pneumonia, pulmonary fibrosis, chronic rheumatoid arthritis, asthma and cutaneous atopy (see abstract). Furthermore, Hamuro et al disclosed in an exemplified working example that  $(\text{NAC})_2$  was effective in inducing oxidative macrophages, and inhibiting delayed type hypersensitivity reaction to ovalbumin antigen. As already stated in the Office Action mailed on 3/23/06 (pages 3-7), it would have been obvious for an ordinary skilled artisan to modify the method of Hamuro et al by using N, N'-diacetylcystine  $[(\text{NAC})_2]$  as an immunosuppressant to suppress a rejection to a minor antigen in an allograft, including a corneal epithelium allograft in a recipient in need thereof in light of the teachings of Hegde et al. and Isseroff et al. because Hegde et al already taught that the relevant immune response during corneal allograft rejection is a donor-specific delayed type hypersensitivity (DTH) reaction; while Isseroff et al also taught methods of treating a damaged or diseased ocular surface by applying a corneal epithelial composite graft to the damaged or diseased ocular surface, wherein the graft comprises a plurality of corneal epithelial cells, including autologous or allogeneic cells. Additionally, an ordinary skilled artisan would have been motivated to carry out the above modification for the following reasons. Firstly,  $(\text{NAC})_2$  is taught to be useful as an immunosuppressant against various human inflammatory immunological diseases by Hamuro et al., and an allograft rejection is considered to be an inflammatory immunological disease. Secondly, it has been shown to inhibit successfully a delayed type hypersensitivity reaction *in vivo* and the DTH reaction has been demonstrated by Hegde et al to be the relevant immune response responsible for corneal allograft rejection. Thirdly, due to the apparent non-toxicity of  $(\text{NAC})_2$  because

Art Unit: 1633

of its inclusion in food (e.g., food for medical care, a health food or a special sanitary food, a toothpaste, a chewing gum and the like), a nutrient (e.g., vitamin and calcium preparations) and an infusion such as a high calory infusion, the use of (NAC)<sub>2</sub> would be free of complications associated with conventional immunosuppressant drugs such as Cyclosporin A as already noted by both Hegde et al. and Isseroff et al. Fourthly, the use of (NAC)<sub>2</sub> as a complication-free immunosuppressant would reduce the rejection of corneal epithelial allografts in a patient in need thereof.

3. With respect to the limitation "wherein the corneal epithelium allograft is an allograft of the whole corneal epithelium" in amended claim 28, please refer to the examiner's interpretation of the claim noted in the 112, second paragraph above. As such the corneal epithelial allograft taught by Isseroff et al contains multi-layered epithelium with corneal epithelial differentiation, including with about 3-5 epithelial cell thickness (see paragraphs 10, 18, 44 and Figure 1) is an allograft of a whole corneal epithelium because normally a corneal surface is also composed of about 5-6 layers of optically regular epithelium (see paragraph 4). Moreover, please also note that a corneal allograft taught by Hegde et al also contains intact corneal epithelial layers or a whole corneal epithelium because cornea contains the superficial corneal epithelium and the corneal stroma.

4. The aforementioned motivations in the above 103 rejection are not general as alleged by Applicants because they are very specific. Furthermore, Applicants fail to provide any reasonable rationales why an ordinary skilled artisan would not have a reasonable expectation of success, particularly in light of the disclosed

Art Unit: 1633

teachings of Hamuro et al., Hegde et al and Isseroff et al. Applicants also fail to state clearly which specific techniques that are not available for an ordinary skilled artisan at the effective filing date of the present application, so that an ordinary skilled artisan would not be able to combine the teachings of Hamuro et al, Hegde et al and Isseroff et al to arrive at the presently claimed invention. Furthermore, Applicants also did not point out specifically which limitation of the presently claimed invention that the combined teachings of Hamuro et al, Hegde et al and Isseroff et al did not teach.

Accordingly, amended claims 21-23, 27-29 and 33-39 are still rejected under 35 U.S.C. 103(a) as being unpatentable over Hamuro et al. in view of Hegde et al. and Isseroff et al. for the same reasons already set forth in the Office Action mailed on 3/23/06 (pages 3-7).

New claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hamuro et al. (EP 1 004 302 A2, IDS) in view of Hegde et al. (Invest. Ophthalmol. Vis. Sci. 41:3341-3347, 2000) and Isseroff et al. (US 2002/0039788 A1) as applied to claims 21-23, 27-29 and 33-39 above, and further in view of Fujll et al. (EP 0812588 A1). ***This is a new ground of rejection necessitated by Applicant's amendment.***

The combined teachings of Hamuro et al., Hegde et al. and Isseroff et al. were discussed and presented above. However, none of the cited references teaches specifically that N, N'-diacetylcystine [(NAC)<sub>2</sub>], the elected substance, is administered in as an eye drop, even though the primary Hamuro et al reference teaches clearly that (NAC)<sub>2</sub> can be included in a drug, a food (e.g., food for medical care, a health food or a

special sanitary food, a toothpaste, a chewing gum and the like), a nutrient (e.g., vitamin and calcium preparations) and an infusion such as a high calory infusion, a physiological saline solution and blood preparations (see abstract; page 2, paragraphs 1-2; page 3, paragraph 10; page 6, paragraph 22).

At the effective filing date of the present application (12/26/00), Fujll et al already taught topical administration of a pharmaceutical composition which aims at inhibiting rejection reactions at organ or tissue transplantation (e.g., the eye or cornea), in various forms, including as an eye drop (see at least the abstract; col. 1, third and last paragraphs; col. 8, line 49 continues to line 15 of col. 9).

Accordingly, it would have been obvious for an ordinary skilled artisan to further modify the method based on the combined teachings of Hamuro et al, Hegde et al. and Isseroff et al. by also administering N, N'-diacetylcystine [(NAC)<sub>2</sub>] in a treated patient as an eye drop to suppress a rejection to a minor antigen in a corneal epithelium allograft in light of the teachings of Fujll et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because topical administration of a pharmaceutical composition in the form of an eye drop to inhibit rejection reactions at organ or tissue transplantation that includes the eye or cornea transplantation was already taught and found to be effective by Fujll et al. Moreover, in light of the overall teachings of Hamuro et al., Hegde et al. Isseroff et al. and Fujill et al., the administration of [(NAC)<sub>2</sub>] as an eye drop into a patient is a simple, straight-forward and direct form of administration.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Hamuro et al., Hegde et al.; Isseroff et al. and Fujll et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

### **Conclusion**

***No claim is allowed.***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Art Unit: 1633


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Dave Nguyen, may be reached at (571) 272-0731.

**To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.**

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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**QUANG NGUYEN, PH.D.**  
**PATENT EXAMINER**